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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/850,293	05/07/2001	Robert Falotico	CRD-0931	2210

27777 7590 05/19/2003

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EXAMINER	
FERKO, KATHRYN P	

ART UNIT	PAPER NUMBER
3743	13

DATE MAILED: 05/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/850,293	FALOTICO, ROBERT	
	Examiner	Art Unit	
	Kathryn Ferko	3743	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

This is a response to the amendment dated April 8, 2003. Claims 1-15 are pending.

Response to Arguments

1. Applicant's arguments filed April 8, 2003 have been carefully reviewed and fully considered.

On page 4 of the office action dated April 8, 2003. Applicant comments, "Vascular remodeling is a different phenomenon than in-stent restenosis. Applicant is making an extraordinarily narrow interpretation. " Firstly, according to the specification on page 10, remodeling is defined as "...a process whose mechanism is not clearly understood but which results in shrinkage of the external elastic lamina and reduction in lumenal area over time, generally a period of *approximately* three to six months in humans." Second, applicant's attention is drawn to Appendix A where "vascular remodeling is a complex set of events involving endothelial cell injury and/or dysfunction that results in intimal/medial thickening." Attention is then drawn to column 4, lines 1-22, column 6, lines 4-10, column 6, lines 55-60, column 7, lines 36-43, column 8, lines 10-16, and column 10, lines 1-11 of Morris et al. in US Patent No. 5,516,781. Morris et al. clearly disclose of preventing the shrinkage of the external elastic lamina and reduction in lumenal area over time in column 6, lines 30-60. Moreover, a period of approximately three to six months in humans is

discussed in column 10, lines 5-16. Therefore, given the specification and a reasonably broad interpretation of the claims would lead to the conclusion that Morris et al. clearly disclose the invention as claimed. Furthermore, applicant's attention is drawn specifically to column 3, lines 45-57, "This invention provides a method of **preventing or treating hyperproliferative vascular disease** in a mammal in need...rapamycin is useful in treating **intimal smooth muscle cell hyperlpasia**, restenosis, and ***vascular occlusion*** in a mammal, particularly following wither **biologically** or mechanically mediated vascular injury, **or under conditions that would predispose a mammal to suffering such a vascular injury**." Occlusion is an obstruction or a closure of a passageway or vessel according to The American Heritage® Dictionary of the English Language, Third Edition copyright © 1992 by Houghton Mifflin Company. Given a reasonably broad interpretation Morris et al. adequately encompasses remodeling and in-lesion lumen loss.

Furthermore, providing a stent with a coating of rapamycin would clearly reduce in-lesion lumen loss both proximate and distal to the medical device. Morris et al. clearly disclose rapamycin delivery via a stent as recited in claim 1 and in applying rapamycin to the stent would clearly affect the area immediate, proximal and distal to the stent.

Moreover, applicant's attention is drawn to Appendix C, where rapamycin is shown to exhibit both anti-proliferative and anti-inflammatory properties.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Morris et al. in US Patent No. 5,516,781.

Morris et al. disclose a method for the prevention of constrictive vascular remodeling via controlled delivery, by release from an intraluminal medical device, a compound having anti-proliferative and anti-inflammatory properties in therapeutic dosage amounts, the compound substantially reducing in-lesion lumen loss both proximate and distal to the intraluminal medical device, as recited throughout the specification and in claims 1-5; utilizing a compound to block the proliferation of fibroblasts in the vascular wall in response to injury, thereby reducing the formation of vascular scar tissue, as recited in column 4, lines 1-32; a compound has rapamycin, as recited in column 3, lines 45-50; and a compound that has analogs and congeners that bind a high-affinity cytosolic protein, FKBP12, and possesses the same pharmacologic properties as rapamycin. Since the current disclosure on page 9 recites, "Rapamycin as used throughout this application **shall include rapamycin**, rapamycin analogs, derivatives and congeners that bind FKBP12 and posses the same pharmacologic properties as rapamycin," the use of rapamycin is all

encompassing. Morris et al. also disclose a compound to affect the translation of certain proteins involved in the collagen formation or metabolism; a drug delivery device having an intraluminal medical device; a therapeutic dosage of an agent releasably affixed to the intraluminal medical device for the treatment of constrictive vascular remodeling; and an intraluminal medical device that is a stent, as recited in claim 1.

Double Patenting

4. Claims 1-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of copending Application No. 09/850,233. Although the conflicting claims are not identical, they are not patentably distinct from each other because the current application is merely a different wording representation. In some aspects the claims of the current application may be broader in some respects and add features in other aspects.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

5. Claims 1-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of copending Application No. 09/850,507. Although the conflicting claims are not identical, they are not patentably distinct from each other because the current application is merely a different wording representation. In some aspects the claims of the current application may be broader in some respects and add features in other aspects.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6. Claims 1-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of copending Application No. 09/850,232. Although the conflicting claims are not identical, they are not patentably distinct from each other because the current application is merely a different wording representation. In some aspects the claims of the current application may be broader in some respects and add features in other aspects.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

7. Claims 1-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim1-14 of copending Application No. 09/850,365. Although the conflicting claims are not identical, they are not patentably distinct from each other because the current application is merely a different wording representation. In some aspects the claims of the current application may be broader in some respects and add features in other aspects.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. Claims 1-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of copending Application No. 09/575,480. Although the conflicting claims are not identical,

they are not patentably distinct from each other because merely a broader representation.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathryn Ferko whose telephone number is (703) 306-3454. The examiner can normally be reached on M-F (7:30-5:00) First Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Henry A Bennett can be reached on (703) 308-0101. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9302 for regular communications and (703) 872-9303 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1113.

Henry Bennett
Supervisory Patent Examiner
Group 3700

KF
May 15, 2003

Appendix A

CHARACTERIZATION OF 3-DIMENSIONAL VASCULAR CELL CO-CULTURES MAINTAINED IN THE ROTATING BIOREACTOR.

D. Ellerson, G.L. Sanford, S.A. Harris-Hooker and C.D. Melhado, Space Medicine & Life Sciences Research Center, Morehouse School of Medicine, Atlanta, GA.

Vascular remodeling is a complex set of events involving endothelial cell injury and/or dysfunction that results in intimal/medial thickening. Although this area has received significant attention, the cellular and molecular mechanisms of vascular remodeling are not completely understood. The development of 3-D co-culture models of the blood vessel will provide a unique opportunity to conduct mechanistic studies into vascular remodeling. We characterized the 3-D growth of endothelial (EC) and smooth muscle (SMC) cells, alone and in co-culture, using the NASA horizontally rotating bioreactor (HRB). Cells were continuously cultured on cytodex-3 microcarriers for up to 30 days (HRB and SF) and were processed for scanning electron microscopy examination, immunocytochemical assessment of phenotypic marker. Controls were maintained in spinner flasks (SF) over the same period. In both systems, microcarriers and cells remain uniformly suspended in the fluid. We found that both EC and SMC grew at a slower rate in the HRB than in the SF. All cultures grew as 3-D aggregates after 14 days. These cultures were positive for the von Willebrand factor (EC) and alpha actin (SMC). The glucose consumption were monitored as an index of cell growth. The cross section for Transmission Electron Micrographs demonstrate the ultrastructural characteristics of SMC and EC. With the large aggregates formed by co-cultures, the surface EC appear to be invaginating, and after 30 days, tube-like structures can be seen in the interior of aggregates. These results suggest that in the HRB, vascular cells spontaneously form 3-D capillary like structures. Hence such cultures may provide a unique model for mechanistic studies of vascular remodeling and angiogenesis.

What is restenosis?

Restenosis (Re"sten-O'sis) is a re-narrowing or blockage of an artery at the same site where treatment, such as an **angioplasty** or **stent** procedure, has already taken place. If restenosis occurs within a stent that has been placed in an artery, it is technically called "in-stent restenosis," the end result being a narrowing in the artery caused by a build-up of substances that may eventually block the flow of blood.

Certificate of Analysis

Rapamycin, Streptomyces hygroscopicus[1 mg] [R1018]

Alternative Product ID: RAPA, Rapamune, Sirolimus, AY-22989, NSC-226080
Description: Antibiotic which demonstrates immunosuppressive properties. It has been shown to block T-cell activation and proliferation, as well as, the activation of p70 S6 kinase. Also anti-inflammatory. Name derived from the native word for Easter Island, Rapi Nui.
Chemical Formula: C51H79NO13
Molecular Weight: M.W. 914.2
Solubility: Soluble in DMSO and Methanol.
CAS Number: CAS [53123-88-9]
Boiling Point / Melting Point: BP/MP: 183-185°C
Active Product: N
Appearance: Yellow Solid
Purity: >98%
Handling: Hygroscopic. Protect from Light and Moisture.
Storage: -20°C.
Shipping: Express Courier
Literature Reference: 1. Merck Index., 1996., 12:, 8288., 2. Vezina, C., et al..
Literature Reference: Purification and Characterization., J. Antibiot., 1975., 28:, 721., 3. Attur, M.G., R. Patel.,.
Literature Reference: Differential anti-inflammatory effects of immunosuppressive drugs: cyclosporin, rapamycin and FK-506 on inducible nitric oxide synthase, nitric oxide, cyclooxygenase-2 and PGE2 production., Inflamm Res., 2000., 49(1):, 20-26..
Bulk Quantity:

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